

# Research Design in *Gray Matters: Integrative Approaches for Neuroscience, Ethics, and Society*

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## I. Introduction

In *Gray Matters: Integrative Approaches for Neuroscience, Ethics, and Society* (*Gray Matters*, Vol. 1), the Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) emphasized that ethics and neuroscience research should be integrated early and explicitly throughout the research endeavor. In that report, the Bioethics Commission concluded that scientists should be equipped to address ethical concerns as they arise. Scientists should engage with ethicists who understand science and technology to design research that accounts for—and can address—relevant ethical considerations. Ethicists should understand the science with which they engage so that they can work with scientists to guide ethically and scientifically rigorous research. The Bioethics Commission recognized that, although some ethical questions are expressed in sharper relief in neuroscience research, integrating ethics explicitly and systematically into research more broadly—across all scientific fields—is crucial because it

allows us to incorporate ethical insights into the scientific process and consider potential societal implications of research from the outset.<sup>1</sup>

## II. Learning Objectives

After completing this activity, students should be able to:

1. Describe the three foundational domains of ethical conduct in scientific research.
2. Discuss various approaches to integrating ethics early and explicitly throughout the research endeavor.
3. Describe how integration of ethics and science promotes ethical research design.

## III. Background

Research design encompasses the entire span of a research project, from its earliest stages, when researchers review other relevant scientific theory and research findings to formulate questions and hypotheses, to the final analyses and disposition of the data.<sup>2</sup> A rigorous research design yields outcomes that have scientific validity (the best approximation to the truth) and reliability (the ability to consistently replicate or reproduce results).<sup>3</sup> A strong research design also uses the appropriate methodology to answer the scientific question at hand.<sup>4</sup>

Contemporary neuroscience comprises many subfields, including molecular neuroscience, cognitive neuroscience, and clinical neuroscience, among others.<sup>5</sup> The many branches of neuroscience address a wide range of topics and encompass a diversity of scientific and ethical questions, but all research will intersect with at least one of three foundational domains of ethical research—professional ethics, research ethics, and consideration of societal implications. Scientists—including neuroscientists—have a responsibility to consider their work thoughtfully within the context of these foundational domains.

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<sup>1</sup> Presidential Commission for the Study of Bioethical Issues (PCSB). (2014, May). *Gray Matters: Integrative Approaches for Neuroscience, Ethics, and Society*. Washington, DC: PCSBI.

<sup>2</sup> Boeije, H.R. (2010). *Analysis in Qualitative Research*. Thousand Oaks, CA: SAGE Publications; Parfrey, P.S., and P. Ravani. (2015). On Framing the Research Question and Choosing the Appropriate Research Design. In P.S. Parfrey and B.J. Barrett. (Eds.). *Clinical Epidemiology: Practice and Methods*, Second Edition (pp. 3-18). New York, NY: Humana Press; USC Libraries. (2015). Organizing Your Social Sciences Research Paper: Types of Research Designs [Webpage]. Retrieved March 20, 2015 from <http://libguides.usc.edu/c.php?g=235034&p=1559832>.

<sup>3</sup> Trochim, W.M.K. (2006). Research Methods Knowledge Base: Introduction to Validity [Webpage]. Retrieved March 20, 2015 from <http://www.socialresearchmethods.net/kb/introval.php>; Trochim, W.M.K. (2006). Research Methods Knowledge Base: Reliability [Webpage]. Retrieved March 20, 2015 from <http://www.socialresearchmethods.net/kb/reliable.php>.

<sup>4</sup> See the *Research Design Background* for more information about ethical research designs. The module is available at <http://www.bioethics.gov/education>.

<sup>5</sup> PCSBI, op cit, p. 4.

## FOUNDATIONAL DOMAINS OF ETHICAL CONDUCT

The foundations for ethical neuroscience research are already in place in the tenets of professional ethics and research ethics, and in early consideration of the societal implications of neuroscience advances. Integration infuses existing codes and models for ethical conduct into the research process from the outset, ensuring that those engaged with neuroscience research are aware of and draw upon these and other applicable ethics frameworks.

*Professional ethics* in science is derived from expectations of responsible conduct of research, codes of conduct, and the character traits that are the hallmark of good scientists. Professional ethics applies throughout the research process, from the reflective articulation of a research question to the honest and responsible communication of scientific findings.

*Research ethics* consists of ethical and regulatory guidelines that govern research, including those concerning research involving humans or animals. Responsible neuroscience includes recognition, interpretation, and application of existing ethical principles and regulations; assurance of compliance with regulations; and consideration of other ethical safeguards for human participants and nonhuman animals in research.

Finally, it is likely that a great deal of neuroscience research will have *societal implications*, including clinical implications, even if findings do not translate immediately into new interventions or technologies. Ethical research requires that scientists consider potential societal implications of their work from the outset.

Source: Presidential Commission for the Study of Bioethical Issues (PCSB). (2014, May). *Gray Matters: Integrative Approaches for Neuroscience, Ethics, and Society*. Washington, DC: PCSBI, p. 14.

## A. Foundational Domains of Ethical Conduct

### 1. Professional Ethics

Professional ethics calls for scientists to act with integrity and promote the responsible conduct of research, avoiding fabrication, falsification, plagiarism, and questionable research practices.<sup>6</sup> Professional ethics principles, which often hold professionals to a higher standard than the general public, can be, but are not always, delineated by professional societies, research institutions, industries, governments, or other entities in the form of codes, guidelines, or

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<sup>6</sup> Steneck, N.H. (2006). Fostering integrity in research: Definitions, current knowledge, and future directions. *Science and Engineering Ethics*, 12(1), 53-74.

policies.<sup>7</sup> For example, the American Psychological Association ethics guidelines consist of a code of conduct, specific ethical standards, and five general principles to help “guide psychologists toward the highest ideals of psychology.”<sup>8</sup> The Society for Neuroscience ethics policy delineates the responsibilities of scientists to ensure the “ethical pursuit of scientific research and the truthful representation of findings.”<sup>9</sup>

Scientists must exhibit high ethical standards when conducting research, collecting and analyzing data, and reporting results. Scientists have a responsibility to act in ways that benefit society.<sup>10</sup> To adhere to professional ethics standards and serve the public, scientists must design and conduct ethical research.

Professional ethics also obligates researchers to honor the trust that colleagues place in them by implementing ethical research design and reporting results honestly.<sup>11</sup> Science is an iterative endeavor in which current and future research builds and relies on previous results. Scientists must rely on the accuracy of interpretations of research findings by their colleagues when designing research protocols.<sup>12</sup> Thus, researchers and society as a whole benefit when scientists adhere to standards of professional ethics.

## 2. Research Ethics

Research ethics is concerned with “the moral problems associated with or that arise in the course of pursuing research” and requires scientists to comply with regulations that govern research with nonhuman animals and human participants.<sup>13</sup> Scientists have an obligation to design research that ensures the proper care and treatment of animals to be used in biomedical and behavioral research. Several regulations and policies govern the ethical use of animals in research.<sup>14</sup> The U.S. Public Health Service (PHS) Policy on Humane Care and Use of Laboratory

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<sup>7</sup> Kovac, J. (2006). Professional Ethics in Science. In D. Baird, E. Scerri, and L. McIntyre. (Eds.). *Philosophy of Chemistry: Synthesis of a New Discipline* (pp. 157-169). Dordrecht, The Netherlands: Springer; Steneck, N.H., op cit.

<sup>8</sup> American Psychological Association. (2010). Ethical Principles of Psychologists and Code of Conduct: Including 2010 Amendments [Webpage]. Retrieved March 20, 2015 from <http://www.apa.org/ethics/code/index.aspx>.

<sup>9</sup> Society for Neuroscience (SfN). (2010). Professional Conduct: SfN Ethics Policy [Webpage]. Retrieved March 20, 2015 from <http://www.sfn.org/member-center/professional-conduct/sfn-ethics-policy>.

<sup>10</sup> Committee on Science, Engineering, and Public Policy; Institute of Medicine; Policy and Global Affairs; National Academy of Sciences, National Academy of Engineering. (2009). *On Being a Scientist: A Guide to Responsible Conduct in Research*, Third Edition. Washington, DC: The National Academies Press, p. 2. Retrieved March 20, 2015 from [http://www.nap.edu/openbook.php?record\\_id=12192](http://www.nap.edu/openbook.php?record_id=12192); Kovac, J., op cit.

<sup>11</sup> Ibid.

<sup>12</sup> Ibid.

<sup>13</sup> Steneck, N.H., op cit, p. 56; PCSBI, op cit, p. 14.

<sup>14</sup> Committee for the Update of the Guide for the Care and Use of Laboratory Animals; Institute for Laboratory Animal Research; Division on Earth and Life Studies; National Research Council. (2011). *Guide for the Care and Use of Laboratory Animals*, Eighth Edition. Washington, DC: The National Academies Press. Retrieved March 20, 2015 from [http://www.nap.edu/openbook.php?record\\_id=12910](http://www.nap.edu/openbook.php?record_id=12910); National Centre for the Replacement Refinement & Reduction of Animals in Research (NC3Rs). (n.d.). The 3Rs: What are the 3Rs? [Webpage]. Retrieved March 20, 2015 from <https://www.nc3rs.org.uk/the-3rs>; National Institutes of Health Office of Extramural Research. (2015).

Animals incorporates the U.S. Government Principles for the Utilization and Care of Vertebrate Animals used in Testing, Research, and Training, and ensures the humane care and use of laboratory animals. It requires that Institutional Animal Care and Use Committees (IACUCs) oversee institutional animal care and use programs. IACUC review and approval are required for all PHS-supported research involving live vertebrate animals. The Office of Laboratory Animal Welfare provides guidance and monitors compliance with the PHS policy.<sup>15</sup> The Institute of Medicine and the National Research Council, and others, have detailed some of the ways in which neuroscience research with animals can advance ethically, including by replacing animals with cell cultures, implementing systematic reviews of existing preclinical and translational animal data, and reducing the number of animals used in research studies through improved experimental design, research methodology, and statistical techniques.<sup>16</sup>

Scientists also have an obligation to design research involving human participants so that it “protect[s] the rights and welfare of individuals who offer themselves for the good of both science and society and, in some cases, for the hope of personal benefit.”<sup>17</sup> Federal regulations and international codes provide guidelines for ethical research with human participants. These include the U.S. Department of Health and Human Services’ (HHS) Federal Policy for the Protection of Human Subjects, Subpart A, which is referred to as the “Common Rule”; the U.S. Food and Drug Administration’s (FDA) Protection of Human Subjects regulations; and the World Medical Association’s Declaration of Helsinki.<sup>18</sup> These regulations and guidelines require that researchers obtain fully informed consent from research participants, minimize risks to participants, and carefully consider the selection of participants, among other protections. They help ensure that research with human participants is designed and deployed with the rights and welfare of participants in mind. The regulations also require that institutional review boards determine that a research design appropriately minimizes risks so that “risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the

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Office of Laboratory Animal Welfare - Public Health Service Policy on Humane Care and Use of Laboratory Animals. Retrieved March 20, 2015 from <http://grants.nih.gov/grants/olaw/references/phspol.htm>; Pankevich, D.E., et al. (2012). *International Animal Research Regulations: Impact on Neuroscience Research. Workshop Summary*. Washington, DC: The National Academies Press. Retrieved March 20, 2015 from [http://www.nap.edu/openbook.php?record\\_id=13322](http://www.nap.edu/openbook.php?record_id=13322).

<sup>15</sup> National Institutes of Health Office of Extramural Research, op cit.

<sup>16</sup> Pankevich, D.E., et al., op cit; Festing, M.F.W. (1994). Reduction of animal use: Experimental design and quality of experiments. *Laboratory Animals*, 28(3), 212-221; Committee on Guidelines for the Use of Animals in Neuroscience and Behavioral Research; Institute for Laboratory Animal Research; Division on Earth and Life Sciences. (2003). *Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research*. Washington, DC: The National Academies Press, pp. 175-180. Retrieved March 20, 2015 from [http://grants.nih.gov/grants/OLAW/National\\_Academies\\_Guidelines\\_for\\_Use\\_and\\_Care.pdf](http://grants.nih.gov/grants/OLAW/National_Academies_Guidelines_for_Use_and_Care.pdf).

<sup>17</sup> PCSBI. (2011, December). *Moral Science: Protecting Participants in Human Subjects Research*. Washington, DC: PCSBI, p. 70.

<sup>18</sup> *Protection of Human Subjects, Department of Health and Human Services (HHS)*. 45 C.F.R. § 46; *Protection of Human Subjects, U.S. Food and Drug Administration (FDA)*. 50 C.F.R. § 21; World Medical Association (WMA). (2013). WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Retrieved March 20, 2015 from <http://www.wma.net/en/30publications/10policies/b3/index.html>.

knowledge that may reasonably be expected to result.”<sup>19</sup> The Office for Human Research Protections maintains regulatory oversight and provides clarification and advice on human subjects research conducted or supported by HHS.<sup>20</sup>

### 3. Societal Implications

Scientists (and the ethicists with whom they engage) are responsible for considering the societal implications of their work when designing research protocols. Because science has the potential to improve human welfare, society is morally obligated to undertake and support scientific research. Scientists pursue knowledge both to advance our understanding of the world and to help solve practical problems. They have a basic duty to pursue these goals for the public good and must consider potential consequences of their work. For example, laboratory researchers studying the connections between neurons in rodent brain slices might contemplate the distal effects—positive and negative—of their findings on humans; this includes considerations about how the results of their well-intended study might lead to unintended applications. Considering the moral responsibility inherent to pursuing research in the public interest, scientists are ethically obligated to consider the impact of their research on individuals and society at large.<sup>21</sup>

## B. Approaches to Ethics Integration in Neuroscience Research Design

Ethics integration supports researchers’ ability to design research that uses appropriate methodology and ensures scientific validity and reliability. Ethics integration occurs when “scientists and ethicists engage with each other, and often other stakeholders, such as communities, to understand the social and ethical dimensions of their work.”<sup>22</sup> Successful ethics integration requires iterative and reflective processes that consider professional and research ethics standards and societal implications throughout the research process to enhance both scientific and ethical rigor.<sup>23</sup> Integration of ethics in research design can “bring ethical decisions and assumptions inherent to the practice of science to the forefront to assess their merits, develop new standards or modify old ones, and reform practices where needed.”<sup>24</sup>

Depending on the type of research, relevant ethical considerations and the approach to ethical integration will vary. For example, a research design for a Phase 3 clinical trial to evaluate a potential new therapy in humans will demand a different level of integration than a design for

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<sup>19</sup> *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.111(a)(2).

<sup>20</sup> Office for Human Research Protection (OHRP). (n.d.). About OHRP: Mission [Webpage]. Retrieved March 20, 2015 from <http://www.hhs.gov/ohrp/about/mission/index.html>.

<sup>21</sup> PCSBI, *op cit*, pp. 14-15.

<sup>22</sup> *Ibid*, p. 12.

<sup>23</sup> *Ibid*.

<sup>24</sup> *Ibid*, p. 15.

studying neurodegeneration in yeast models.<sup>25</sup> Whatever the protocol, multiple approaches to ethics integration are available for promoting ethical research design.

In *Gray Matters*, Vol. 1, the Bioethics Commission highlighted several approaches to ethics integration. One foundational approach is to expose scientists to ethics education and ethicists to science education early and throughout their professional careers. Ethical research design also can be facilitated through integrating ethics in structures and processes at the institutional level. For example, institutions can convene an independent panel of ethicists to consult with researchers about ethical considerations in research design. Funders might support ethics integration by directing funds to study the ethical, legal, and social implications of research they support. Another approach is ethics integration through research ethics consultation. Research consultation services can provide ethics advice to scientists considering ethical implications of their research. Integrating ethics into research design also can be accomplished by engaging with stakeholders, who might include members of the public, industry representatives, scientists, policymakers, patients, research participants, community members, and funders, among others. Finally, ethics integration can be achieved by directly including on the research team or protocol an ethicist, or a scientist experienced in ethics. The Bioethics Commission acknowledged that these examples are not exhaustive and recommended evaluation of existing and innovative approaches to ethics integration.<sup>26</sup>

## C. Bioethics Commission Recommendations

Of the four recommendations the Bioethics Commission made in *Gray Matters*, Vol. 1, the first pertains directly to ethical research design. Ethical issues arise throughout research, and scientists should prepare for them when planning and conducting research. Researchers have an “obligation to identify and address ethical issues encountered in their work and a broader obligation to support scientific research that furthers the public good.”<sup>27</sup> Integrating ethics can help address ethical questions as they arise and “cultivate an ethical sensibility beyond the bounds of the case at hand.”<sup>28</sup>

### **Recommendation 1:**

#### **Integrate Ethics Early and Explicitly Throughout Research**

**Institutions and individuals engaged in neuroscience research should integrate ethics across the life of a research endeavor, identifying the key ethical questions associated with their research and taking immediate steps**

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<sup>25</sup> Ibid, p. 13.

<sup>26</sup> Ibid, pp. 16-27.

<sup>27</sup> Ibid, p. 25.

<sup>28</sup> Ibid.



**to make explicit their systems for addressing those questions. Sufficient resources should be dedicated to support ethics integration.**<sup>29</sup>

## IV. Reading

For the purposes of discussion, students should download and read the following Bioethics Commission materials (reports are available for download on the Bioethics Commission's website at [www.bioethics.gov](http://www.bioethics.gov) under "Projects"):

*Gray Matters: Integrative Approaches for Neuroscience, Ethics, and Society*, pp. 12-25 ("Approaches to Ethics Integration in Neuroscience").

## V. Discussion Questions

The following questions are based on the information provided above and through the indicated reading and are intended to reinforce important aspects of ethical research design and ethics integration that are highlighted in *Gray Matters*, Vol. 1. Important points are noted with each question to help the instructor guide group discussion. The "Additional Resources" section is a helpful source in answering these questions.

### 1. What are the three foundational domains of ethical conduct of research and what do they encompass?

Starting points for discussion:

- a. *Professional ethics* in science is derived from expectations of responsible conduct of research, codes of conduct, and the character traits that are the hallmark of good scientists. Professional ethics applies throughout the research process, from the reflective articulation of a research question to the honest and responsible communication of scientific findings.
- b. *Research ethics* consists of ethical guidelines and regulations that govern research, including those concerning research involving humans or animals. Responsible neuroscience includes recognition, interpretation, and application of existing ethical principles and guidelines; assurance of compliance with regulations; and consideration of other ethical safeguards for nonhuman animals and human participants in research.
- c. Neuroscience research often has *societal implications*, including clinical implications, even if findings do not translate immediately into new interventions or technologies.

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<sup>29</sup> Ibid.



Ethical research requires that scientists consider potential societal implications of their work from the outset.

## **2. How do the three foundational domains of ethical conduct support ethical research design?**

Starting points for discussion:

- a. Adhering to professional ethics standards obligates researchers to implement ethical research design and report results accurately to honor the trust that colleagues place in them. Professional ethics also requires that scientists design research that fulfills their obligation to pursue work for the public good.
- b. Research ethics supports ethical research in specific types of neuroscience research, such as research using nonhuman animals or human participants. Regulations and guidance outline necessary protections for use of nonhuman animals in research. Review by an IACUC helps advise researchers how to avoid or replace the use of animals; reduce the number of animals used per study; and refine methods to minimize animals' pain, suffering, or distress. In addition, scientists design their research involving human participants to protect the rights and welfare of the participating individuals. Regulations and guidelines outline necessary protections, which include obtaining fully informed consent from research participants, minimizing risk to participants, and carefully considering the selection of participants. These protections help ensure that research with human participants is designed and deployed with the rights and welfare of individuals in mind.
- c. Considering societal implications of their work encourages scientists to implement research designs that will be most beneficial and least harmful to individuals and to society. Research designs that recognize societal implications also help to maintain public trust in science, which is crucial for scientific progress.

## **3. How does integrating ethics early and throughout research support ethical research design?**

Starting points for discussion:

- a. Ethics integration requires scientists, ethicists, and often other stakeholders, to work together to understand the societal and ethical dimensions of their work and facilitate research. Ethics integration allows scientists and ethicists to consider professional and research ethics standards and societal implications iteratively and reflectively when designing research and throughout the research process.
- b. To facilitate a deeper understanding of professional and research ethics and the societal implications of science, scientists and future scientists should be exposed to

ethics early in their education and careers. Ethics education for scientists and science education for ethicists can equip both groups of scholars with the training to recognize and assess ethical concerns while adhering to scientific rigor in research design.

## VI. Problem-Based Learning

**Scenario A.** *Neurodegenerative diseases impose a major global public health burden. Until recently, research on neurodegeneration was restricted to relating the clinical observation of the disease among humans to pathology in postmortem human brain tissue. Advances in research and identification of genetic mutations contributing to the cause of neurodegenerative diseases have led to creation of cellular and animal models of neurodegeneration. Today, many laboratory researchers studying neurodegeneration choose a simple organism, such as yeast, for their disease model.*<sup>30</sup>

The following additional reading might be useful in considering this scenario:

Khurana, V., and S. Lindquist. (2010). Modelling neurodegeneration in *Saccharomyces cerevisiae*: Why cook with baker's yeast? *Nature Reviews Neuroscience*, 11(6), 436-449. Retrieved March 20, 2015 from <http://lindquistlab.wi.mit.edu/PDFs/Khurana2010NRN.pdf>.

### 1. Why is yeast an acceptable model of human neurodegenerative diseases? What are its limitations?

Starting points for discussion:

- a. Yeast and humans share certain genes and fundamental cell biological processes.
- b. The yeast model is amenable to analysis. Yeast reproduces quickly and is easy to grow. Yeast also is genetically tractable; its DNA can be manipulated, replaced, removed, or augmented.
- c. In this case, yeast replaces the use of animals in research.
- d. Yeast research is complementary to animal and human subjects research, but research with yeast, a unicellular organism, cannot comprise *all* of neurodegeneration research.

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<sup>30</sup> Khurana, V., and S. Lindquist. (2010). Modelling neurodegeneration in *Saccharomyces cerevisiae*: Why cook with baker's yeast? *Nature Reviews Neuroscience*, 11(6), 436-449.

## **2. What ethical questions regarding research design might laboratory researchers encounter while studying neurodegeneration in yeast?**

Starting points for discussion:

- a. Researchers might consider which research methodology will yield the most scientifically valid and reliable results.
- b. Researchers might consider which research designs will most easily translate from yeast to animal models, and eventually to research with human participants.
- c. Researchers might consider how engaging with stakeholders, such as members of the public, industry representatives, scientists, policymakers, patients, research participants, community members, and funders can enhance their research design.

## **3. Which of the foundational ethical domains are relevant to studying neurodegeneration in yeast?**

Starting points for discussion:

- a. Laboratory researchers studying neurodegeneration in yeast models might routinely encounter questions of professional ethics, such as those related to analytic integrity, authorship, or mentorship of postdoctoral fellows, among others. All researchers must avoid fabrication, falsification, plagiarism, and questionable research practices.
- b. All researchers are responsible for considering the potential societal implications of their research, such as how the results of a well-intended study might yield unintended applications. For example, researchers should consider how experimental findings might lead to unintended malevolent applications.

**Scenario B.** *Deep brain stimulation (DBS) is a surgical intervention that delivers rapidly fluctuating electric current to deep brain structures. It is approved by the FDA to treat Parkinson's disease, essential tremor, dystonia, and severe obsessive-compulsive disorder. The exact mechanism of DBS action is unknown, but it remains a viable treatment option for certain disorders and is being investigated for potential to treat disorders of mood, behavior, and thought, such as depression. In 2007, bioethicists, patient advocates, policymakers, psychiatrists, neurologists, and other experts met to establish consensus regarding the standards and protections that should be in place to facilitate the ethical practice of DBS research for disorders of mood, behavior, and thought.*<sup>31</sup>

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<sup>31</sup> Rabins, P., et al. (2009). Scientific and ethical issues related to deep brain stimulation for disorders of mood, behavior and thought. *Archives of General Psychiatry*, 66(9), 931-937.

The following additional reading might be useful in considering this scenario:

Rabins, P., et al. (2009). Scientific and ethical issues related to deep brain stimulation for disorders of mood, behavior and thought. *Archives of General Psychiatry*, 66(9), 931-937. Retrieved March 20, 2015 from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2753479/>.

## **1. What were the goals of the consensus conference?**

Starting points for discussion:

- a. To engage affected parties—including researchers, patient advocates, policymakers, psychiatrists, neurologists, bioethicists, and other experts—in a deliberative discussion to facilitate the ethical practice of DBS research.
- b. To establish a consensus about the design of future clinical trials of DBS for disorders of mood, behavior, and thought.
- c. To develop standards to protect the human participants in DBS clinical trials.

## **2. What were the reasons for convening a conference dedicated to the ethical design of DBS research?**

Starting points for discussion:

- a. Neurosurgical intervention for disorders of mood, behavior, and thought has a troubled history. Despite sparse evidence of efficacy and little effort to evaluate side effects, lobotomy surgery was performed on 20,000 people in the United States by 1950.<sup>32</sup> Integrating ethical considerations into research design can facilitate research by reducing the likelihood of ethical pitfalls, increasing the acceptability of DBS research, and enhancing the probability that DBS research will result in promising new therapies.
- b. Individuals with psychiatric disorders or conditions sometimes can be vulnerable to exploitation in research as a result of potentially impaired consent capacity, coercion, or undue social influence. Research among vulnerable populations requires special safeguards for research participants. Potential protections can include specialized informed consent processes or rigorous and careful participant selection procedures.

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<sup>32</sup> Ibid.

### 3. Which approach to ethics integration did this conference reflect?

Starting points for discussion:

- a. The conference was a model of stakeholder engagement. Bioethicists, patient advocates, policymakers, psychiatrists, neurologists, and other experts convened to discuss ethical design of DBS research.
- b. The conference also resembled the strategies of research ethics consultation services and the inclusion of an ethics perspective on the research team.

## VII. Exercises

**Exercise A.** *Some researchers experiment with neuroimaging techniques to explore the possibility of detecting lies, preventing crimes, or making inferences about criminal intent. In the following referenced study, researchers asked their participants to steal either a ring or a watch and then deny stealing either of the objects when asked. Participants answered questions, some of which were intended to prompt denial of stealing, while undergoing functional magnetic resonance imaging (fMRI) to assess changes in brain activity. Using the fMRI data, the researchers built models to detect deception. One model correctly detected deceit in 90 percent of participants.*<sup>33</sup>

The following reference provides useful information:

Kozel, F.A., et al. (2005). Detecting deception using functional magnetic resonance imaging. *Biological Psychiatry*, 58(8), 605-613. Retrieved March 20, 2015 from [http://www.researchgate.net/publication/7578089\\_Detecting\\_deception\\_using\\_functional\\_magnetic\\_resonance\\_imaging/links/00b4951b5f6244e0e2000000](http://www.researchgate.net/publication/7578089_Detecting_deception_using_functional_magnetic_resonance_imaging/links/00b4951b5f6244e0e2000000).

1. What societal implications might research related to deception raise?
2. Is projecting the meaning of results in these studies to real-world scenarios ethical?
3. Design a proposal or slide presentation for this research study that highlights the points at which the three ethical domains might be incorporated into research design.

**Exercise B.** *In 1993, the National Institutes of Health (NIH) mandated the inclusion of women in all NIH-funded human clinical trials. Previously, women often were excluded from clinical trials, creating a gap in knowledge about the safety and efficacy of treatments among female patients. As a consequence, women sometimes experienced unexpected side effects from new*

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<sup>33</sup> Kozel, F.A., et al. (2005). Detecting deception using functional magnetic resonance imaging. *Biological Psychiatry*, 58(8), 605-613.

*treatments. Female animal models are still underused in laboratory research because of fears that reproductive cycles confound research results and are difficult to monitor. The sex disparity early in the research process can result in negative repercussions for women's health. For example, researchers have much less knowledge of how certain drugs affect women, compared with men.*<sup>34</sup>

The following references provide useful information:

Clayton, J.A., and F.S. Collins. (2014). Policy: NIH to balance sex in cell and animal studies. *Nature*, 509(7500), 282-283. Retrieved March 20, 2015 from <http://www.nature.com/news/policy-nih-to-balance-sex-in-cell-and-animal-studies-1.15195>.

Rabin, R.C. (2014, May 14). Labs are told to start including a neglected variable: Females. *New York Times*. Retrieved March 20, 2015 from [http://www.nytimes.com/2014/05/15/health/nih-tells-researchers-to-end-sex-bias-in-early-studies.html?\\_r=0](http://www.nytimes.com/2014/05/15/health/nih-tells-researchers-to-end-sex-bias-in-early-studies.html?_r=0).

Prendergast, B.J., Onishi, K.G., and I. Zucker. (2014). Female mice liberated for inclusion in neuroscience biomedical research. *Neuroscience & Biobehavioral Reviews*, 40, 1-5. Retrieved March 20, 2015 from <http://www.sciencedirect.com/science/article/pii/S0149763414000049>.

- 1. How might the exclusion of females in research protocols reflect poor research design? What are the societal implications? When might exclusion of females be appropriate ethically?**
- 2. How does NIH plan to address the underrepresentation of female animals in biomedical research?**
- 3. How would the integration of ethics into the research endeavor ensure adequate research design and inclusion of female animals in future research protocols?**
- 4. Left-handed individuals are often excluded from fMRI studies because of the presumed differences in brain structure and function from right-handed individuals. Consider the parallels between these research designs and those that exclude females.**

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<sup>34</sup> Clayton, J.A., and F.S. Collins. (2014). Policy: NIH to balance sex in cell and animal studies. *Nature*, 509(7500), 282-283; Rabin, R.C. (2014, May 14). Labs are told to start including a neglected variable: Females. *New York Times*. Retrieved March 20, 2015 from [http://www.nytimes.com/2014/05/15/health/nih-tells-researchers-to-end-sex-bias-in-early-studies.html?\\_r=0](http://www.nytimes.com/2014/05/15/health/nih-tells-researchers-to-end-sex-bias-in-early-studies.html?_r=0); Prendergast, B.J., Onishi, K.G., and I. Zucker. (2014). Female mice liberated for inclusion in neuroscience biomedical research. *Neuroscience & Biobehavioral Reviews*, 40, 1-5.

## VIII. Glossary of Terms

**Common Rule:** Current federal regulations that protect research participants, codified by the U.S. Department of Health and Human Services in the Code of Federal Regulations at 45 C.F.R. Part 46, Subpart A. Also known as “Human Subjects Regulations.”

**Community engagement:** A mechanism to involve members of the community in the planning and execution of research, inclusive of those who will be affected by or who are in a position to influence the course of research.

**Informed consent:** The process of informing and obtaining permission from an individual before conducting medical or research procedures or tests.

**Protocol:** A plan for the conduct of a research project, including all aspects of the project from recruitment to obtaining informed consent to dissemination of results.

**Vulnerable populations:** Groups of individuals who are potentially unable to exercise control over how their interests are represented and pursued.

## IX. Additional Resources

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